REMARKS

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Comments regarding restriction requirement

Claims 4, 7, 9, 10, 13, 18 and 19 are "method of making" and "method of use" claims which all ultimately depend from product claim 3. Therefore, upon allowance of claim 3, it is believed that claims 4, 7, 9, 10, 13, 18 and 19 should be rejoined and considered, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)." See also MPEP § 821.04 Rejoinder which states:

> if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claims will be rejoined.

Utility rejection of claims 3, 5-6, 8, 11-12 and 14-17 under 35 U.S.C. §§ 101 and 112, first paragraph

Claims 3, 5-6, 8, 11-12 and 14-17 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that "the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility or a well established utility."

The rejection of claims 3, 5-6, 8, 11-12 and 14-17 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is identified in the patent application as an antibody that specifically binds to growth-associated protease inhibitor heavy chain precursor (GAPIP), which is a polypeptide encoded by a gene that is expressed in reproductive, gastrointestinal, nervous, and fetal tissues (see the

Specification, e.g., at p. 16, lines 16-22 and p. 28, lines 12-14). The novel polypeptide GAPIP to which the claimed antibody specifically binds is demonstrated in the Specification to be a member of the protease inhibitor family (see the Specification at pp. 14-15), whose biological functions include regulation of the activity and effect of proteases and control pathogenesis of proteolytic disorders, and in treatment of HIV (see the Specification at p. 2, lines 21-23). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

The fact that the polypeptide to which the claimed antibody specifically binds is a member of the protease inhibitor family alone demonstrates utility beyond the reasonable probability required by law. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds also have patentable utility, regardless of their actual function. The law has never required a patentee to prove more.

There is, in addition, direct proof of the utility of the claimed invention. Applicants submit with this response the Declaration of Lars Michael Furness describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic affect of a drug candidate (Furness Declaration at ¶ 10).

The Patent Examiner does not dispute that the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Instead, the Patent Examiner contends that the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds cannot be useful without precise

knowledge of its function. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Furness Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in the absence of any knowledge as to the precise function of the protein. The uses of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not

grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Uses of the claimed antibodies for diagnosis of conditions or disorders characterized by expression of GAPIP, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Furness Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The Specification discloses that the SEQ ID NO:1 is GAPIP and therefore there is an asserted utility for the claimed antibodies

The Examiner alleges that nowhere is it disclosed in the instant specification that SEQ ID NO:1 is GAPIP and, therefore, technically there is no asserted utility for the claimed antibodies (see Office Action at p. 3). Such, however, is not the case. For example, in the Brief Description of the Figures, it is explicitly stated that "Figures 1A, 1B, 1C, 1D, 1E, 1F, 1G, 1H, 1I, and 1J show the amino acid sequence (SEQ ID NO:1) and nucleic acid sequence (SEQ ID NO:2) of GAPIP." See the Specification at page 5, lines 2-3. Similar statements identifying SEQ ID NO:1 as an amino acid sequence of GAPIP can be found throughout the Brief Description of the Figures at page 5, lines 5-11.

B. The similarity of the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to another of undisputed utility demonstrates utility

Because there is a substantial likelihood that the claimed GAPIP is functionally related to human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3, polypeptides of undisputed utility, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed, and readily apparent from the patent application, that the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds shares more than 40 % sequence identity

over 70 amino acid residues with human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3. For example, over the 70 amino acid residues from G271 to I340 of SEQ ID NO:1, human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 are 55%, 48% and 54% identical, respectively. This is more than enough homology to demonstrate a reasonable probability that the utility of human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 is, accordingly, very high.

The Examiner must accept the Appellants' demonstration that the homology between the claimed invention and human pre-inter-α-trypsin inhibitor, human pre-inter-α-trypsin inhibitor heavy chain H1, and pre-inter-α-trypsin inhibitor heavy chain H3 demonstrates utility by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

C. The uses of the claimed antibody and the SEQ ID NO:1 polypeptide to which the antibody specifically binds for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Furness Declaration. There is no dispute that the claimed invention is in fact a useful tool in two-dimensional polyacrylamide gel electrophoresis ("2-D PAGE") analysis and western blots used to monitor protein expression and assess drug toxicity.

The instant application, Serial No. 09/828,423, filed on April 5, 2001 (hereinafter "Hillman '423 application"), is a divisional of and claims priority to U.S. application Serial No. 09/388,774 filed September 2, 1999, issued May 8, 2001 as U.S. Patent No. 6,228,991, which is a divisional application and claimed priority to U.S. application Serial No. 09/074,579 filed May 7, 1998, issued December 14, 1999 as U.S. Patent No. 6,001,596 (hereinafter "the Hillman '579 application"), all having the identical specification., with the exception of corrected typographical errors and reformatting.

In his Declaration, Mr. Furness explains the many reasons why a person skilled in the art who read the Hillman '579 application on May 7, 1998 would have understood that application to disclose the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to be useful for a number of gene and protein expression monitoring applications, *e.g.*, in 2-D PAGE technologies, in connection with the development of drugs and the monitoring of the activity of such drugs. (Furness Declaration at, e.g., ¶¶ 9-13). Much, but not all, of Mr. Furness' explanation concerns the use of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds in the creation of protein expression maps using 2-D PAGE.

2-D PAGE technologies were developed during the 1980's. Since the early 1990's, 2-D PAGE has been used to create maps showing the differential expression of proteins in different cell types or in similar cell types in response to drugs and potential toxic agents. Each expression pattern reveals the state of a tissue or cell type in its given environment, *e.g.*, in the presence or absence of a drug. By comparing a map of cells treated with a potential drug candidate to a map of cells not treated with the candidate, for example, the potential toxicity of a drug can be assessed (see Furness Declaration at ¶ 10).

The claimed invention makes 2-D PAGE analysis a more powerful tool for toxicology and drug efficacy testing. A person of ordinary skill in the art can derive more information about the state or states or tissue or cell samples from 2-D PAGE analysis with the claimed invention than without it. As Mr. Furness explains:

> In view of the Hillman '579 application, the Wilkins article, and other related pre-May 7, 1998 publications, persons skilled in the art on May 7, 1998 clearly would have understood the Hillman '579 application to disclose the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds to be useful in 2-D PAGE analyses for the development of new drugs and monitoring the activities of

drugs for such purposes as evaluating their efficacy and toxicity . . . . (Furness Declaration, ¶ 10)

* * *

Persons skilled in the art would appreciate that a 2-D PAGE map that utilized the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds would be a more useful tool than a 2-D PAGE map that did not utilize this protein sequence in connection with conducting protein expression monitoring studies on proposed (or actual) drugs for treating reproductive, developmental, neoplastic, and immunological disorders for such purposes as evaluating their efficacy and toxicity. (Furness Declaration, ¶ 12)

Mr. Furness' observations are confirmed in the literature published before the filing of the patent application. Wilkins, for example, describes how 2-D gels are used to define proteins present in various tissues and measure their levels of expression, the data from which is in turn used in databases:

> For proteome projects, the aim of [computer-aided 2-D PAGE] analysis . . . is to catalogue all spots from the 2-D gel in a qualitative and if possible quantitative manner, so as to define the number of proteins present and their levels of expression. Reference gel images, constructed from one or more gels, for the basis of two-dimensional gel databases. (Wilkins, Tab C, p. 26).

D. The use of proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling using polypeptides are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Furness in his Declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, *et al.*, Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 1):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Reference No. 1, page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (Reference No. 2); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (Reference No.3).

The more genes – and, accordingly, the polypeptides they encode -- that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding (Reference No. 4). Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be withdrawn.

E. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes). (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the GAPIP sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated only as a result of Incyte's discovery of the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by alleging that the disclosed and well-established utilities for the claimed antibody and the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds are not a specific and substantial asserted utility, credible asserted utility or well-established utility" (see Office Action at p. 2). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The Precise Biological Role Or Function Of An Expressed Polypeptide Is Not Required To Demonstrate Utility

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a 2-D gel or western blot to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the applicant provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d at 1359, but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d at 1366. If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Furness Declaration (at, *e.g.*, ¶¶ 9-13), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at

all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged as much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for the SEQ ID NO:1 polypeptide to which the claimed antibody specifically binds, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polypeptide is a member of the protease inhibitor family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the protease inhibitor family to GAPIP. In the Office Action, the Patent Examiner takes the position that unless Appellants can identify which particular biological function within the class of protease inhibitors is possessed by GAPIP, utility cannot be imputed. To demonstrate utility by membership in the class of protease inhibitors, the Examiner would require that all protease inhibitors possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class

possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a substantial number of useless members. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members, *e.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).[1]

The Examiner addresses GAPIP as if the general class in which it is included is not the protease inhibitor family, but rather all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the protease inhibitor family does not. The protease inhibitor family is sufficiently specific to rule out any reasonable possibility that GAPIP would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the protease inhibitor class of proteins has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the GAPIP encoded by the claimed polypeptide is useful.

Even if the Examiner's "common utility" criterion were correct – and it is not – the protease inhibitor family would meet it. It is undisputed that known members of the protease inhibitor family regulate the activity and effect of proteases. A person of ordinary skill in the art need not know any more about how the claimed invention regulates the activity and effect of proteases to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given protease inhibitor regulates the activity and effect of proteases. The Examiner then goes on to

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[1]At a recent Biotechnology Customer Partnership Meeting, PTO Senior Examiner James Martinell described an analytical framework roughly consistent with this analysis. He stated that when an applicant's claimed protein "is a member of a family of proteins that already are known based upon sequence homology," that can be an effective assertion of utility.

assume that the only use for GAPIP absent knowledge as to how this member of the protease inhibitor family actually works is further study of GAPIP itself.

Not so. As demonstrated by Applicants, knowledge that GAPIP is a protease inhibitor is more than sufficient to make it useful for the diagnosis and treatment of cancer and immune disorders. Indeed, GAPIP has been shown to be expressed in cancer and immune cells. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

C. The uses of GAPIP in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, 8th Edition, August 2001, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely

because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

Such beneficial uses beyond studying the claimed invention itself have been demonstrated, in particular those described in the Furness Declaration. The Furness Declaration demonstrates that the claimed invention is a tool, rather than an object, of research, and it demonstrates exactly how that tool is used. Without the claimed invention, it would be more difficult to generate information regarding the properties of tissues, cells, drug candidates and toxins apart from additional information about the polypeptide itself.

The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include uses drug screening (e.g., Specification at page 38).

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

The Office Action has also set forth the novel theory that the central dogma of molecular biology (*i.e.*, DNA directs transcription of messenger RNA which in turn directs translation of protein) somehow does not apply to the discoveries of the present application. That is, the nucleotide sequence of SEQ ID NO:2 (which encodes the polypeptide of SEQ ID NO:1) was determined from a human uterus cDNA library. That cDNA library in turn was made from messenger RNA isolated from human tissue. See the Specification, for example, at pages 38-39. Thus, the nucleotide sequences of the present invention are expressed sequences. The Office Action purports that the existence of an expressed mRNA does not insure that the protein encoded by the mRNA will be translated and, hence, the claimed subject matter lacks patentable utility.

Regulation of gene expression occurs at many levels, including transcription, splicing, polyadenylation, mRNA stability, mRNA transport and compartmentalization, translation efficiency, protein modification, and protein turnover. While steady state mRNA levels are not always directly

proportional to the amount of protein produced in a cell, mRNA levels are **routinely** used as an indicator of protein expression. Countless scientific publication have been based on data relating to mRNA levels when the polypeptide encoded by the mRNA was unknown or difficult to detect. Moreover, mRNA levels are **usually** a good indicator of protein levels in a cell. The Office Action cites an example of inhibition of translation initiation; however, this example represents a comparatively unusual mechanism of gene regulation. According to B. Lewin [(1997) Genes VI Oxford University Press, Inc. New York, NY] (pages enclosed):

> Transcription of a gene in the active state is controlled at the stage of initiation, that is, by the interaction of RNA polymerase with its promoter. This is now becoming susceptible to study in the *in vitro* systems... ***For most genes, this is a major control point; probably it is the most common level of regulation.*** [page 847, emphasis added].
>
> But having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that ***the overwhelming majority of regulatory events occur at the initiation of transcription. Regulation of tissue-specific gene transcription lies at the heart of eukaryotic differentiation.*** [pages 847-848, emphasis added]

Thus the question is not whether there is the potential for post-transcriptional regulation of SEQ ID NO:1 expression but whether one skilled in the art would have a reasonable expectation that SEQ ID NO:1 expression correlates with the levels of SEQ ID NO:2 mRNA. Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. 519, 532, 148 USPQ 689 (1966). In the case of the instant invention, one skilled in the art would be imprudent in assuming, *a priori*, that protein levels did not correspond to mRNA levels and that levels of SEQ ID NO:1 were controlled predominantly in a post-transcriptional manner, thereby dismissing the significance of mRNA levels. Inasmuch as the predictive value of mRNA levels applies to the "utility" of Applicants' invention, Applicants request withdrawal of the rejection.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Appellant is not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

Enablement rejections under 35 U.S.C. §112, first paragraph

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

In addition, claims 20, 22, 24, 27, 28, 30-35 and 43-46 have been rejected as failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph, because the Specification allegedly does not describe how to make the claimed antibodies. The Office Action does not dispute that the present application describes how to make an antibody which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1. See pages 6-7 of the Office Action of June 17, 2002. However, the Office Action alleges that the present disclosure does not describe how to make (a) an antibody which specifically binds to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1; (b) an antibody which specifically binds to a biologically-active fragment of the amino acid sequence of SEQ ID NO:1; or (c) an antibody which specifically binds to an immunogenic fragment of the amino acid sequence of SEQ ID NO:1. Such, however, is not the case.

While not conceding the propriety of the Patent Office position, claim 3 has been revised so as to no longer recite an antibody which specifically binds to a biologically-active fragment of SEQ ID NO:1. This amendment has been made solely to expedite prosecution of the subject application. Issues pertaining to such antibodies have therefore been rendered moot.

The Office Action does not appear to dispute that conventional methods for making antibodies could be used to make antibodies which specifically bind to a polypeptide comprising a naturally occurring amino acid sequence at least 90% sequence identical to the amino acid sequence of SEQ ID NO:1 or to immunogenic fragments of SEQ ID NO:1. Instead, the Office Action asserts that the present disclosure is deficient because one of skill in the art would not be able to make the variant polypeptides and immunogenic fragments of SEQ ID NO:1 *per se* and, hence, without the variant polypeptides and immunogenic fragments, one would not be able to make antibodies which specifically

bind to those variant polypeptides and immunogenic fragments. On the contrary, the Specification is sufficient in this regard.

Note that claim 3 recites not only that the variant polypeptides are at least 90% identical to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of GAPIP) and SEQ ID NO:2 (the polynucleotide sequence encoding GAPIP), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

> As used herein, the term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent (e.g., formamide), temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.
>
> For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium

citrate, 1% SDS, 50 % formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.
(Specification at page 12, line 12 to page 13, line 12)

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding GAPIP or closely related molecules may be used to identify nucleic acid sequences which encode GAPIP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding GAPIP, allelic variants, or related sequences. (Specification at page 34, lines 2-8)

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the GAPIP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:2 or from genomic sequences including promoters, enhancers, and introns of the GAPIP gene. (Specification at page 34, lines 9-12)

See also Example VI at pages 44-45.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or

highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims. Conventional methods for making antibodies, such as those described at pages 26-28 of the Specification, could then be used to make antibodies which specifically bind to the recited polypeptide variants.

Accordingly, the Abaza et al. document cited in the Office Action relating to structure-function relationships in proteins is simply not germane to whether one can make and use the polypeptide variants recited by the present claims. That is, regardless of the precise functional characteristics of the SEQ ID NO:1 variants, one can still make those polypeptide variants, and antibodies which specifically bind to the variants, using the disclosure provided by the present Specification. The antibodies could then be used in, for example, diagnostic testing, drug discovery, expression profiling, etc. (See, e.g., Furness Declaration, attached.)

Furthermore, the Examiner's attention is also directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078) (Reference No. 5). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

Claim 3 recites, *inter alia*, antibodies which specifically bind to "a polypeptide comprising . . . a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as growth-associated protease inhibitor heavy chain precursors and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "90% variants" recited by the present claims have a variation that is far less than that of all potential growth-associated protease inhibitor heavy chain precursors related to SEQ ID NO:1, i.e., those growth-associated protease inhibitor heavy

chain precursors having as little as 30% identity over at least 150 residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a growth-associated protease inhibitor heavy chain precursor.

Furthermore, the Office Action has asserted that one of skill in the art could not make and use an isolated antibody which specifically binds an immunogenic fragment of SEQ ID NO:1. Such, however, is not the case.

At pages 14-15, the Specification describes the polynucleotide of SEQ ID NO:2, the polypeptide encoded by that polynucleotide, *i.e.*, SEQ ID NO:1, and chemical and structural characteristics thereof. The polypeptide and fragments thereof can be produced by either recombinant means (see, *e.g.*, the Specification at pages 18-23) or by chemical synthesis (see, *e.g.*, the Specification at page 18, lines 15-26; and page 23, lines 27-31). As discussed at length above in connection with the "utility" rejection, the use of antibodies and the polypeptides to which they specifically bind for diagnosis of diseases, for toxicology testing, and for drug discovery are well known in the art, *e.g.*, via the use of expression profiling. Such uses are also described in the Specification, *e.g.*, at pages 33-38. Hence, the requirement for providing objective enablement has been met.

The Examiner questions, in particular, whether the present Specification provides sufficient guidance to enable the identification of immunogenic fragments of SEQ ID NO:1. The Specification is fully sufficient in this regard.

First note that at page 8, lines 5-6, "immunologically active" is defined as "the capability of the natural, recombinant, or synthetic GAPIP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies." Specific binding is further defined at page 12 as meaning:

> . . . that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

Methods of producing specifically binding antibodies are described, for example, at pages 26-28. In this regard, note the paragraph at page 27, lines 3-9, which describes fragment sizes of GAPIP for raising antibodies. See also page 48 which describes the production of antibodies to fragments of GAPIP, including the description of how to identify appropriate immunogenic sites of GAPIP:

> . . . the GAPIP amino acid sequence is analyzed using LASERGENE software to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel supra, ch. 11.) (Specification at page 48, lines 24-28)

The Examiner has failed to provide reasons as to why one would doubt that the methods disclosed in the present Specification would allow one to identify immunogenic fragments of SEQ ID NO:1.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement***. [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited antibodies which specifically bind to the variants and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established.

For at least the above reasons, withdrawal of this rejection is requested.

Written description rejection under 35 U.S.C. §112, first paragraph

Claims 3, 5, 6, 8, 11, 12 and 14-17 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being based on a Specification which provides an inadequate written description of what is claimed. The Office Action appears to urge that every single member of the claimed genus of polypeptides "and the antibodies that bind these fragments and variants" must be specifically disclosed by the Specification, otherwise an inadequate written description has been set forth. However, such a disclosure is not required for an adequate written description.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*
> *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

a) The specification provides an adequate written description of the claimed "variants" and "fragments" of SEQ ID NO:1

The subject matter encompassed by claims 3, 5, 6, 8, 11, 12 and 14-17 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" and "fragment" language of independent claim 23 recites an isolated antibody which specifically binds to a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1", or "an immunogenic fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:1." The polypeptide sequence of SEQ ID NO:1 is explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:1 are described in the Specification at, for example, page 3, lines 4-5; page 6, lines 2-5 and 9-15; and page 15, lines 12-15. Fragments of SEQ ID NO:1 are described in the Specification at, for example, page 3, lines 4-5; page 4, lines 2-4; and page 7, lines 1-7.

One of ordinary skill in the art would recognize polypeptide sequences which are variants at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art recognize whether it was a variant of SEQ ID NO:1. Similarly, SEQ ID NO:1 provides the blueprint to describe any immunogenic fragment thereof. Accordingly, the Specification provides an adequate written description of the recited variants and fragments of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA, and antibodies which specifically bind to those proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polypeptides in terms of chemical structure, rather than functional

characteristics. For example, the language of independent claim 3 recites chemical structure to define the claimed genus:

> 3. An isolated antibody which specifically binds to a polypeptide selected from the group consisting of:
>
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
>
> b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally-occurring amino acid sequence encoding a polypeptide having protease inhibitor activity, and
>
> c) an immunogenic fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the claimed antibodies and the polypeptides to which they specifically bind. The antibodies and the polypeptides to which they specifically bind defined by the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Examiner failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant". Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078)(of record). Through exhaustive

analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to antibodies which specifically bind to polypeptides related to human growth-associated protease inhibitor heavy chain precursor (GAPIP). In particular, the polypeptides are selected from amino acid sequences comprising SEQ ID NO:1, naturally occurring amino acid sequences at least 90% identical to SEQ ID NO:1, or immunogenic fragments of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as human growth-associated protease inhibitor heavy chain precursor (GAPIP) proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polypeptide comprising "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 942 amino acid residues). This variation is far less than that of all potential GAPIP proteins related to SEQ ID NO:1, i.e., those GAPIP proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of May 7, 1998. Much has happened in the development of recombinant DNA technology in the 19 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polypeptide variants and fragments at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 3, 5-6, 8, 11-12 and 14-17 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Claim 1 has been placed in independent form. In addition, "comprising" language has been used in the claims, as suggested by the Examiner. Withdrawal of this rejection is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Please charge Deposit Account No. 09-0108 in the amount of $400.00 as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108.

Respectfully submitted,

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Date: 18 November 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The paragraph beginning at line 2 of page 1 has been amended as follows:

This application is a divisional application of U.S. application Serial No. 09/388,774 filed September 2, 1999, now U.S. Patent No. 6,228,991, which is a divisional application of U.S. application Serial No. 09/074,579 filed May 7, 1998, [issued December 14, 1999 as] now U.S. Patent No. 6,001,596, all of which applications and patents are hereby incorporated by reference herein.

IN THE CLAIMS

Claims 1 and 2 have been cancelled.

Claims 3, 4, 10-13, 15, 18 and 19 have been amended as follows:

3. (Once Amended) An isolated antibody which specifically binds to a polypeptide [of claim 1] selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally-occurring amino acid sequence encoding a polypeptide having protease inhibitor activity, and

c) an immunogenic fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

4. (Once Amended) A diagnostic test for a condition or disease associated with the expression of GAPIP in a biological sample, the method comprising [the steps of]:

a) combining the biological sample with an antibody of claim 3, under conditions suitable for the antibody to bind the polypeptide and form an antibody: polypeptide complex; and

b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

10. (Once Amended) A method of preparing a polyclonal antibody with the specificity of the antibody of claim 3, the method comprising:

a) immunizing an animal with a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response;

b) isolating antibodies from said animal; and

c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

11. (Once Amended) [An] A polyclonal antibody produced by a method of claim 10.

12. (Once Amended) A composition comprising the polyclonal antibody of claim 11 and a suitable carrier.

13. (Once Amended) A method of making a monoclonal antibody with the specificity of the antibody of claim 3, the method comprising:

a) immunizing an animal with a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response;

b) isolating antibody producing cells from the animal;

c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells;

d) culturing the hybridoma cells; and

e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

15. (Once Amended) A composition comprising the monoclonal antibody of claim 14 and a suitable carrier.

18. (Once Amended) A method for detecting a polypeptide comprising the amino acid sequence of SEQ ID NO:1 in a sample, the method comprising [the steps of]:

a) incubating the antibody of claim 3 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and

b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide comprising the amino acid sequence of SEQ ID NO:1 in the sample.

19. (Once Amended) A method of purifying a polypeptide comprising the amino acid sequence of SEQ ID NO:1 from a sample, the method comprising:

a) incubating the antibody of claim 3 with a sample under conditions to allow specific binding of the antibody and the polypeptide; and

b) separating the antibody from the sample and obtaining the purified polypeptide comprising the amino acid sequence of SEQ ID NO:1.

Claims 20 and 21 have been added as follows:

20. (New) An isolated antibody of claim 3, which specifically binds to an immunogenic fragment having at least 15 contiguous amino acid residues of a polypeptide comprising the amino acid sequence of SEQ ID NO:1.

21. (New) An isolated antibody of claim 3, which specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.